

# Thymic Rejuvenation Protocol

Tesamorelin · Thymosin  $\alpha_1$  · Rapamycin · Imeglimin · DHEA

*Evidence-based combinatorial strategy for thymic fat reversal and T-cell regeneration*

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**Research and informational use only.** This document describes a theoretical protocol derived from published primary literature. No clinical trial has tested this specific combination. All interventions require physician supervision, baseline cancer screening, and ongoing monitoring. Nothing herein constitutes medical advice.

## Executive Summary

The thymus involutes progressively after the first decade of life, replacing functional thymic epithelial cells (TECs) with adipose tissue and reducing naive T-cell output. Partial reversal of this process was demonstrated in the 9-subject TRIIM trial (Fahy et al., 2019) using recombinant human GH, DHEA, and metformin. The present protocol replaces rhGH with tesamorelin (FDA-approved GHRH analogue; preserves pituitary feedback), replaces metformin with imeglimin (no GH-axis antagonism; direct TEC mitochondrial protection), adds thymosin  $\alpha_1$  for direct T-cell maturation support, and integrates weekly rapamycin exclusively in the one-week tesamorelin-free window. The result is nine components and one repeating 4-week cycle with no conditional logic.

#	Component	Dose	Frequency	Phase
1	DHEA	25-50 mg	Daily	All phases
2	Imeglimin	500-1000 mg	Daily	All phases
3	Zinc + Copper	Zn 20-25 mg + Cu 2 mg	Daily	All phases
4	Vit D3 + K2	D3 3000-5000 IU + K2 150 mcg	Daily	All phases
5	Omega-3 (EPA+DHA)	2-3 g	Daily	All phases
6	Melatonin	0.3 mg	Bedtime	All phases
7	Tesamorelin	2 mg SC	Nightly	Weeks 1-3 of 4
8	Thymosin a1	1.6 mg SC	2x/week	All weeks
9	Rapamycin	5 mg oral	1x/week (Mon)	Week 4 only

## Background: Thymic Aging and the Case for Intervention

The thymus is the primary lymphoid organ generating naive T lymphocytes. Thymopoietic output peaks in the first decade then declines ~3% per year. By the sixth decade, >70% of functional thymic parenchyma has been replaced by adipose tissue. The downstream consequences are clinically significant: reduced TCR diversity, contraction of the naive T-cell compartment, expansion of terminally differentiated effector memory cells, and declining vaccine responsiveness — all hallmarks of immunosenescence.

### The TRIIM Trial: Proof of Concept

Fahy et al. (2019, *Aging Cell*) demonstrated in 9 healthy men (51-65 years) that a one-year protocol of rhGH + DHEA + metformin produced: (i) reduced thymic adipose on MRI; (ii) increased sjTREC (marker of recent thymic emigrants); (iii) increased naive CD4<sup>+</sup>/CD8<sup>+</sup> T cells; (iv) mean epigenetic age reversal of 2.5 years (Horvath clock). Underpowered (n=9, no control arm), it nonetheless provided the first mechanistic framework for pharmacological thymic rejuvenation.

### Rationale for Protocol Modifications

- **rhGH to Tesamorelin:** rhGH bypasses the hypothalamic-pituitary axis and produces non-pulsatile IGF-1 elevation with documented risks (oedema, insulin resistance). Tesamorelin preserves somatostatin feedback, produces physiological GH pulses, and directly reduces visceral/ectopic fat (FDA Phase 3 validated, n=806).
- **Metformin to Imeglimin:** Metformin suppresses GH secretion via STAT3 inhibition and upregulates IGFBP-2, reducing free IGF-1 — antagonising the protocol's primary signal. Imeglimin achieves metabolic control through mitochondrial respiratory chain rebalancing with no GH-axis antagonism, and its ROS-reduction mechanism is directly relevant to aged TEC biology.
- **Thymosin  $\alpha_1$  added:** While tesamorelin rebuilds the TEC niche, thymosin  $\alpha_1$  supports T-cell maturation within it via a complementary, non-redundant mechanism on thymocyte differentiation and MHC-II expression.
- **Rapamycin in clearance week only:** mTORC1 is essential for TEC proliferation. Continuous rapamycin causes thymic atrophy. By administering rapamycin only during the tesamorelin-free week, senescent stromal cell clearance occurs without antagonising TEC mTOR signalling during the three thymopoietic weeks.

## Daily Base Stack (All Phases, Year-Round)

Six components taken every day regardless of cycle phase, providing foundational TEC support, anti-inflammaging activity, and metabolic buffering throughout.

Component	Dose	Timing	Rationale
DHEA	25-50 mg	Morning	Androgen receptor on TECs; insulin sensitisation; original TRIIM component
Imeglimin	500-1000 mg	With dinner	Mitochondrial ROS reduction in TECs; GSIS enhancement; no GH-axis antagonism
Zinc + Copper	Zn 20-25 mg + Cu 2 mg	Morning	Thymulin cofactor; copper mandatory to prevent depletion from zinc supplementation
Vit D3 + K2	D3 3000-5000 IU + K2 150 mcg	With fat, morning	VDR signalling on TECs; K2 (MK-7) prevents vascular Ca misdeposition
Omega-3 (EPA+DHA)	2-3 g	With meals	NF-kB / NLRP3 inflammasome suppression in thymic stroma
Melatonin	0.3 mg	30 min before sleep	MT1/MT2 receptors on TECs; somatostatin suppression enhances tesamorelin GH pulse

**Zinc-copper ratio:** Long-term zinc above 20 mg/day without copper supplement causes copper-deficiency anaemia and neurological effects. The 2 mg/day copper co-supplement is mandatory whenever zinc is taken at these doses.

## The 4-Week Repeating Cycle

Every 4-week cycle is structurally identical. No conditional scheduling. The daily base stack runs uninterrupted throughout all weeks.

Week	Phase	Active (beyond daily base)	Rationale
1	THYMOPOIESIS	Tesamorelin 2 mg SC nightly Thymosin a1 1.6 mg SC (Tue+Fri)	IGF-1-driven TEC proliferation + T-cell maturation
2	THYMOPOIESIS	Tesamorelin 2 mg SC nightly Thymosin a1 1.6 mg SC (Tue+Fri)	Sustained; the ~3-week thymocyte maturation cycle spans weeks 1-3
3	THYMOPOIESIS	Tesamorelin 2 mg SC nightly Thymosin a1 1.6 mg SC (Tue+Fri)	Sustained GH pulse; minimum meaningful thymopoietic window
4	CLEARANCE	Tesamorelin PAUSED Thymosin a1 1.6 mg SC (Tue+Fri) Rapamycin 5 mg oral (Mon, fasted)	mTOR inhibition w/ no active IGF-1 signal; autophagy + senescent stromal cell clearance

### Cycle Architecture Notes

- **Why 3 thymopoietic weeks?** The ETP-to-naive-T-cell journey takes ~3 weeks. Two weeks would be below the minimum biologically meaningful thymopoietic window.
- **Why rapamycin only in week 4?** IGF-1 activates TECs via PI3K/Akt/mTORC1. Concurrent rapamycin would directly block this. Pausing tesamorelin during the rapamycin week eliminates the antagonism while preserving the senolytic benefit.
- **Why thymosin  $\alpha_1$  continuous?** It acts via MAPK/NF- $\kappa$ B (mTOR-independent), making it safe alongside rapamycin. Continuous dosing maximises T-cell maturation support and eliminates cycling complexity.
- **Annual tesamorelin exposure:**  $3/4 \times 365 = \sim 274$  days/year — equivalent to or slightly above seasonal 4-6 month blocks used in TRIM-style protocols.
- **Rapamycin frequency:** ~13 doses/year (every 4 weeks) is consistent with published intermittent longevity-dosing regimens and avoids continuous immunosuppression.

## Component Deep-Dives

### 1. Tesamorelin (GHRH Analogue)

Full-length (44 aa) synthetic GHRH analogue with N-terminal trans-3-hexenoic acid modification conferring DPP-IV resistance (~30-38 min half-life). Activates pituitary somatotrophs with preserved somatostatin feedback, producing physiological GH pulses. Primary FDA-validated effect: visceral fat reduction 10-18% over 26-52 weeks (Phase 3, n=806). Directly targets ectopic adipogenesis driving thymic involution. FDA-approved as Egrifta (2010) and Egrifta SV (2025) for HIV-associated lipodystrophy.

Parameter	Detail
Dose/schedule	2 mg SC nightly (weeks 1-3 of every 4-week cycle; paused week 4)
Common AEs	Injection-site pruritus (~7.6%); peripheral oedema (~6.1%); arthralgia; nausea
Glucose	Modest glucose/HbA1c increase; directly offset by imeglimin GSIS enhancement
IGF-1 monitoring	Every 3 months; target upper-normal for age 29; alert if >300 ng/mL
Cancer data	Phase 3 52-week trials: no significant difference vs. placebo for new cancers
Contraindications	Active malignancy; disrupted H-P axis; pregnancy

### 2. Thymosin a1 (Endogenous TEC Peptide)

Endogenous 28-aa peptide secreted by TECs. Promotes T-cell maturation from double-negative thymocytes, enhances MHC-II expression on TECs, upregulates CD25/CD28 on developing thymocytes, and activates TLR9 on dendritic cells. Additive to tesamorelin (different receptor class, different mechanism). Best safety profile of all add-ons: >11,000 subjects, 30+ trials, no dose-limiting toxicities. Safe alongside rapamycin (mTOR-independent mechanism).

Parameter	Detail
Dose/schedule	1.6 mg SC, Tuesday + Friday; continuous all 4 weeks including clearance week
Common AEs	Mild injection-site reactions; no systemic toxicities at therapeutic doses
mTOR interaction	None - MAPK/NF-kB pathway; fully compatible with rapamycin
Regulatory	Zadaxin: approved in Asia/Middle East; US/EU: investigational/compounded

### 3. Rapamycin (mTORC1 Inhibitor)

Allosteric mTORC1 inhibitor via FKBP12. In aged thymic stroma: (i) induces autophagy clearing damaged organelles/proteins; (ii) suppresses constitutively active mTORC1 in senescent stromal cells, suppressing their SASP. Administered only in week 4 (tesamorelin paused) to avoid antagonising TEC mTOR proliferation. PEARL trial (2025, n=114, 1 year, 5 mg/week): broadly safe; Mannick 2014 showed 20% vaccine response improvement with rapalog at comparable dosing.

Parameter	Detail
Dose/schedule	5 mg oral, Monday morning fasted; week 4 of every 4-week cycle (~13 doses/year)
Glucose	Mild insulin signalling impairment; buffered by imeglimin
Common AEs (5 mg/week)	Mouth ulcers; GI effects; lipid changes; generally mild at this dose
Monitor	CBC every 6 months for lymphopenia; discontinue if significant lymphocyte drop
Contraindications	Active serious infection; strong CYP3A4 inhibitors (azole antifungals); pregnancy
Regulatory	FDA-approved Rapamune for transplant; off-label for longevity

### 4. Imeglimin (Glimin Class, Japan-Approved)

First-in-class glimin (Twymeeg, Japan 2021). Dual mechanism: (i) mitochondrial respiratory chain rebalancing (partial Complex I inhibition + Complex III correction) reducing ROS; (ii) direct GSIS amplification from pancreatic beta-cells via incretin enhancement. Replaces metformin in this protocol because: no GH-axis antagonism; stronger mitochondrial ROS protection relevant to TEC biology; GSIS enhancement specifically offsets glucose elevation from tesamorelin and rapamycin.

**Critical evidence gap:** All imeglimin RCT data is from type 2 diabetic patients. Its safety in normoglycaemic healthy adults is entirely unstudied. Hypoglycaemia from GSIS enhancement in euglycaemic individuals is a real theoretical concern. Close glucose monitoring mandatory. Access outside Japan requires off-label sourcing.

Parameter	Detail
Dose/schedule	500-1000 mg oral with dinner; titrate from 500 mg
Glucose interaction	Offsets tesamorelin and rapamycin glucose effects; monitor fasting glucose quarterly
Renal	Renally cleared; dose review eGFR <45; contraindicated eGFR <30
Common AEs	Diarrhoea (~10%); milder GI profile than metformin
Key gap	Zero controlled data in healthy normoglycaemic adults
Regulatory	Japan only (Twymeeg); not approved US/EU/UK

## Key Pharmacological Interactions

Combination	Interaction	Verdict
Tesamorelin + Imeglimin	Tesamorelin raises glucose (GH-IR); imeglimin GSIS is directly compensatory	Synergistic
Tesamorelin + Rapamycin	IGF-1 activates TEC mTOR; rapamycin blocks mTOR. Direct antagonism if concurrent	Resolved by cycling: rapamycin week 4 only
Tesamorelin + Thymosin a1	Different receptor classes; independent pathways	Additive, no interaction
Tesamorelin + Melatonin	Low-dose melatonin suppresses somatostatin, enhancing nocturnal GH pulse	Mildly synergistic
Rapamycin + Thymosin a1	Thymosin a1 acts via MAPK/NF-kB (mTOR-independent)	Compatible, additive
Rapamycin + Imeglimin	Rapamycin impairs insulin signalling; imeglimin GSIS buffering is specifically relevant	Complementary
Rapamycin + DHEA	No significant PK interaction at 5 mg rapamycin	Compatible
Zinc + Copper	High-dose zinc displaces copper over months causing anaemia/neuropathy	Co-supplement 2 mg Cu/day mandatory
Imeglimin + Vit D3	Imeglimin renally cleared; no interaction with Vit D metabolism	Compatible
Melatonin + Tesamorelin	Take 0.3 mg melatonin 30-60 min after tesamorelin injection	Compatible; minor timing

## Monitoring Framework

In the absence of clinical trial data, rigorous monitoring is not optional — it is the only mechanism distinguishing benefit from harm in an N-of-1 context.

Biomarker	Frequency	Interpretation / Action
IGF-1 (serum)	Every 3 months	Draw end of week 3 (peak exposure). Target: upper-normal for age 29. Alert >300 ng/mL: reduce dose
HbA1c + fasting glucose	Every 3 months	Tesamorelin + rapamycin both raise glucose; imeglimin buffers. Alert: HbA1c trend >5.7%
sjTREC (qPCR, PBMCs)	Every 6 months	Primary direct measure of thymic output; expect detectable increase by month 6-12
Naive CD4+/CD8+ T cells (flow)	Every 6 months	Peripheral correlate of thymopoiesis
CBC + differential	Every 6 months	Watch for lymphopenia (rapamycin); pause if significant lymphocyte drop
eGFR / creatinine	Every 6 months	Imeglimin dose review if eGFR <45; contraindicated <30
25-OH-Vitamin D	Every 6 months	Adjust D3 to maintain 40-60 ng/mL
IGFBP-3 (serum)	Every 6 months	IGF-1/IGFBP-3 molar ratio: more sensitive mitogenic risk index than IGF-1 alone
DNAm epigenetic clock (GrimAge)	Annually	Composite biological age; most sensitive to 12-month interventions
Thymic MRI (chest)	Annually	Gold standard structural measure of thymic fat reversal
Fasting lipids + hsCRP	Every 6 months	SASP surrogate; expect hsCRP decline with anti-inflammatory daily stack
PSA (men) + cancer screening	Annually	IGF-1 elevation is contraindicated in active malignancy

## Limitations and Evidence Gaps

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**Non-negotiable clinical caveat:** This protocol is an extrapolation from mechanistic first principles and the TRIIM trial. No published RCT has tested this specific combination. Each component has independent safety data, but their combined interaction in healthy middle-aged adults is entirely uncharacterised. Physician supervision with endocrinology and immunology input is required before initiating any component of this protocol.

**No combination trial data.** The 9-component protocol has never been tested in a controlled study. Individual safety profiles are extrapolated to the combination without interaction data.

**Imeglimin in healthy adults.** All imeglimin RCTs enrolled T2DM patients. Its pharmacokinetics, GSIS effects, and safety in normoglycaemic individuals are entirely unstudied. Hypoglycaemia from GSIS enhancement in euglycaemia is a real theoretical risk requiring close monitoring.

**Imeglimin access outside Japan.** Only approved in Japan as of 2026. Outside Japan, access requires off-label channels, compounding, or clinical trial enrolment — each with distinct legal and quality-control implications.

**TRIIM limitations propagate.** The entire biological rationale ultimately rests on a 9-subject, single-arm trial plus mechanistic data. No larger controlled replication exists.

**Long-term cancer surveillance gap.** Tesamorelin Phase 3 (52 weeks) showed no cancer signal. Long-term IGF-1 elevation data in healthy adults is unavailable. Elevated cancer risk is an absolute contraindication.

**Loss of metformin pleiotropic benefits.** Metformin has substantial evidence for cancer risk reduction, cardiovascular protection, and epigenetic age slowing (TAME trial). Imeglimin has none of this data.

**Regulatory and access variability.** Tesamorelin (US: FDA, off-label), thymosin a1 (US: compounded; Asia: approved), rapamycin (off-label longevity), imeglimin (Japan only). Legal access differs by jurisdiction.

## Key References

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- [1] Fahy GM et al. (2019). Reversal of epigenetic aging and immunosenescent trends in humans. *Aging Cell* 18(6):e13028. doi:10.1111/ace1.13028
- [2] Katlun J et al. (2025). PEARL Trial: rapamycin in healthy adults. PMC12074816. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC12074816/>
- [3] Mannick JB et al. (2014). mTOR inhibition improves immune function in the elderly. *Sci Transl Med* 6(268):268ra179. doi:10.1126/scitranslmed.3009892
- [4] Palmer CS et al. (2022). Caloric restriction reverses age-related thymic involution (CALERIE). *Science* 375(6581):671-677. doi:10.1126/science.abg7292
- [5] Imeglimin dual mechanism on insulin secretion and sensitivity. PMC12992193. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12992193/>
- [6] Imeglimin vs. metformin on incretin/insulin secretion (RCT, 2025). PMC11701202. <https://pmc.ncbi.nlm.nih.gov/articles/PMC11701202/>
- [7] Metformin inhibits GH secretion via STAT3 in pituitary cells. PMC5514928. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5514928/>
- [8] Falutz J et al. (2010). Tesamorelin Phase 3 pivotal trial. *N Engl J Med*. doi:10.1056/NEJMoa0907004
- [9] mTOR essential for TEC development and thymic function. PMC5915037. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5915037/>
- [10] FGF21 modulates mTOR in TECs across lifespan. *Nature Aging* 2024. <https://www.nature.com/articles/s43587-024-00801-1>
- [11] Zhang W et al. Thymosin a1 clinical review (>30 trials). *Int Immunopharmacol*. doi:10.1016/j.intimp.2018.06.042
- [12] Imeglimin mitochondrial mechanism and AMPK activation. PMC9839736. <https://pmc.ncbi.nlm.nih.gov/articles/PMC9839736/>